

¹¹C-Acetate can be Used in Place of ¹⁸F-Fluorodeoxyglucose for Positron Emission Tomography Imaging of Non-small Cell Lung Cancer with Higher Sensitivity for Well-Differentiated Adenocarcinoma

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Objectives: Although positron emission tomography (PET) using ¹⁸F-fluorodeoxy-glucose (FDG) frequently gives false-negative results for slow-growing tumors, ¹¹C-acetate (AC)-PET has been reported to be able to detect them. To determine the usefulness of AC-PET for imaging non-small cell lung cancers (NSCLCs), the sensitivity and specificity were compared between the AC-PET and FDG-PET with a multicenter study.

Materials and Methods: A total of 284 pulmonary lesions (227 NSCLCs and 57 benign lesions) were examined using both AC-PET and FDG-PET before surgery at seven Japanese institutes. The AC- or FDG-uptake in each lesion were quantitatively measured using the contrast ratio of the standard uptake value between the lesions and the contralateral lung.

Results: The sensitivity of AC-PET for diagnosing NSCLC was 0.71, which was significantly higher than the value of 0.57 obtained by FDG-PET ($p < 0.001$). No significant difference in the specificity was seen between AC- and FDG-PET. For the 146 well-differentiated adenocarcinomas, the sensitivity of AC-PET was 0.62, which was significantly higher than the value of 0.37 obtained by FDG-PET ($p < 0.001$). Of the 51 moderately- or poorly-differentiated adenocarcinomas and 30 nonadenocarcino-

mas, there was no significant difference of sensitivity between AC- and FDG-PET.

Conclusions: AC-PET could be used in place of FDG-PET for imaging NSCLC, with higher sensitivity for well-differentiated adenocarcinoma compared with FDG-PET.

Key Words: Positron emission tomography, Acetate, Fluorodeoxy-glucose, Non-small cell lung cancer, Lung adenocarcinoma.

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Recent advances in positron emission tomography (PET) using ¹⁸F-fluorodeoxy-glucose (FDG) have contributed significantly to the ability to differentiate between non-small cell lung cancer (NSCLC) and benign pulmonary nodules. Nevertheless, FDG-PET sometimes gives false-negative results, particularly for well-differentiated (W/D) adenocarcinoma because of their low glucose metabolism.^{1–4} We previously reported that 60% of W/D adenocarcinomas less than 3 cm in size failed to be identified by FDG-PET.² Therefore, other PET tracers should be used for the imaging of W/D adenocarcinoma of the lung.

Radio-labeled acetate (AC) has long been used to examine lipid and cholesterol synthesis in biochemistry.^{5,6} Clinically, ¹¹C-AC has been widely used as a PET tracer to evaluate myocardial oxidative metabolism.^{7,8} Recently, ¹¹C-AC has also been reported to be a useful PET tracer for imaging of slow-growing tumors that cannot be visualized by FDG-PET, such as W/D hepatocellular carcinoma, prostate cancers, and thymoma.^{9–11} We previously reported that AC-PET was able to image 8 of 22 (36%) W/D adenocarcinomas that could not be visualized by FDG-PET.¹² In the present study, to examine the diagnostic usefulness of AC-PET for NSCLC, the sensitivity and specificity for the discrimination between NSCLC and benign nodules were compared between the AC-PET and FDG-PET in patients with NSCLC recruited with a multicenter study.

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MATERIALS AND METHODS

Eligibility

The study protocol was to perform AC-PET and FDG-PET in patients with lung adenocarcinomas or lesions suspected of lung adenocarcinomas before surgery. The study was approved by the ethical committee of each of the seven institutes involved in the study (see Appendix). Informed consent was obtained from all patients after a discussion of the risks and benefits of the study with their surgeons.

Patients

Between April 2005 and December 2007, a total of 248 patients with 284 pulmonary lesions larger than 1 cm in size, who were suspected of or diagnosed as having lung adenocarcinomas, prospectively underwent both AC-PET and FDG-PET before surgery. The final diagnosis of the 284 lesions were NSCLC in 227 and benign nodules in 57 (Table 1). The histologic types of the 227 NSCLCs were W/D adenocarcinoma in 146 lesions, moderately-differentiated (M/D) or poorly-differentiated (P/D) adenocarcinomas in 51, and nonadenocarcinomas in 30. The histologic types of the 30 nonadenocarcinomas were squamous cell carcinoma in 27, adenosquamous carcinoma in 2, and large cell carcinoma in 1. Of the 57 benign nodules, 20 were acute inflammations, 32 were old inflammations, and the remaining 4 were benign tumors. The 32 old inflammatory lesions were incidentally found away from lung cancers and were diagnosed clinically as old inflammations without histologic examination based on the following reasons: (1) a review of retrospective chest radiograph or computed tomography (CT) examinations performed before surgery (mean observation period, 41 ± 23 months; range, 24–97 months) revealed that the sizes of the lesions had remained unchanged, and (2) postoperative follow-up CT examinations showed that the sizes of the lesions had remained unchanged for more than 12 months (mean follow-up period, 16 ± 2 months; range, 12–20 months). Therefore, the sizes of the 32 old inflammatory nodules had remained unchanged for more than 36 months throughout the preoperative and postoperative periods. The other 18 acute

inflammatory lesions, 4 benign tumors, and 227 NSCLCs were histologically diagnosed using the resected specimens.

Preparing of ^{11}C -Acetate

^{11}C -AC was prepared according to the method reported by Ishiwata et al.,¹³ which was based on the guidelines for synthesis and quality control of PET tracer by the Japanese Isotope Association. Production of AC was carried out by using a ^{11}C multipurpose synthesizer at the two PET centers, i.e., C-11-BII (Sumitomo Heavy Industries Ltd., Tokyo) at Nishidai Clinic in Tokyo and AMMC-05 (JFE Engineering Corporation, Tokyo) at Japanese Red Cross Kumamoto Health Care Center in Kumamoto, Japan.

PET Scanning

PET scanning was performed at Nishidai Clinic and Japanese Red Cross Kumamoto Health Care Center by using a POSICAM.HZL mPOWER scanner (Positron Co., Houston, TX) and an Advance Nx (GE Medical Systems, United Kingdom), respectively. The PET parameters in the former were as follows: transmission scan, 1 minute/bed; emission scan, 2 minutes/bed; bed positions, eight beds; and field of view, 16.2 cm in z axis with 12 cm in overlap. Those parameters in the latter were as follows: emission scan, 3 minutes/bed; bed position, eight beds; and field of view, 15.7 cm in z axis with 12 cm in overlap. The AC- and FDG-PET examinations were performed on the same day within 1 month before surgery, according to a previously reported protocol.¹² Briefly, ^{11}C -AC at a dose of 125 $\mu\text{Ci/kg}$ (4.6 MBq/kg) was administered first. PET imaging was performed approximately 10 minutes after the administration of ^{11}C -AC. Approximately 60 minutes after AC-PET imaging, ^{18}F -FDG at a dose of 125 $\mu\text{Ci/kg}$ (4.6 MBq/kg) was administered, ensuring a gap of at least 120 minutes between the administration of ^{11}C -AC and that of ^{18}F -FDG, i.e., more than six decay half-lives of ^{11}C (20 minutes). FDG-PET imaging was performed approximately 60 minutes after the administration of FDG. It took approximately 3 hours in total to examine both AC- and FDG-PET.

PET Data Analysis

PET images were reviewed by each one radiologist at the two PET centers (Uno and Nakashima with respective 34 and 20 years of experience for diagnosing radioisotope scintigraphy and PET). After image reconstruction, a two-dimensional circular region of interest (ROI) (1.0–6.9 cm in diameter) was drawn surrounding the lesions with positive findings. For the lesions with negative and faintly positive PET findings, the ROI was drawn on the fusion image with the corresponding CT to measure their standard uptake value (SUV). The AC- and FDG-uptake were calculated by the contrast ratio of SUV (SUV-CR) between the lesion and the contralateral lung, as described previously.^{2,3} Briefly, the values of maximum SUV (SUV-max) in the tumor ROI (T) and in the corresponding point of contralateral normal lung ROI (N) were then measured. The SUV-CR was calculated according to the formula of T/N for each lesion as an index of AC or FDG uptake.

TABLE 1. Characteristics of Pulmonary Nodules

Non-small cell lung cancer (<i>n</i> = 227)	
Mean size (range) (cm)	2.0 \pm 1.0 (1.0–6.0)
Histologic subtype	
W/D adenocarcinoma	146
M/D or P/D adenocarcinoma	51
Nonadenocarcinoma	30
Benign nodules (<i>n</i> = 57)	
Mean size (range) (cm)	1.7 \pm 1.2 (1.0–6.9)
Histologic type	
Active inflammation	20
Old inflammation	32
Benign tumor	5

W/D, well-differentiated; M/D, moderately-differentiated; P/D, poorly-differentiated.

Pathologic Diagnosis by Central Review

Unstained slide glasses were obtained in all cases and processed by routine hematoxylin and eosin staining and Elastica-van Gieson staining. The histologic sections were reviewed by two pathologists at Kumamoto University Hospital (Iyama and Honda with 34 and 22 years, respectively, of experience making pathologic diagnoses), who were unaware of the patients' clinical data. The histologic types of NSCLC were classified according to the World Health Organization classification.^{14,15} A consensus was reached if any difference in their opinions existed.

Determining the Cutoff Values of SUV-CR

The cutoff values for discrimination between NSCLC and benign nodules were determined using a receiver operating characteristics (ROC) curve that was constructed using SPSS software (SPSS 15.0 J for Windows, SPSS, Chicago, IL). The value with the highest sensitivity and the highest specificity was determined as the cutoff value on the ROC curve. Lesions with higher SUV-CR than cutoff value were defined as positive on AC- or FDG-PET result.

Statistical Analysis

The true-positive (TP), true-negative (TN), false-positive (FP), and false-negative (FN) results of the AC- and FDG-PET images were compared with the pathologic diagnoses. Sensitivity was calculated as $TP/TP + FN$ and specificity as $TN/TN + FP$; differences between the AC- and FDG-PET results were analyzed using the McNemar test. The differences in the positive rates among the histologic types were analyzed using a χ^2 test. The differences in SUV-CR values among the histologic subtypes of NSCLC were analyzed using the Fisher's exact test. These statistical analyses were performed using the SPSS software. Values of p less than 0.05 were considered significant. All values in the text and tables are given as the mean \pm SD.

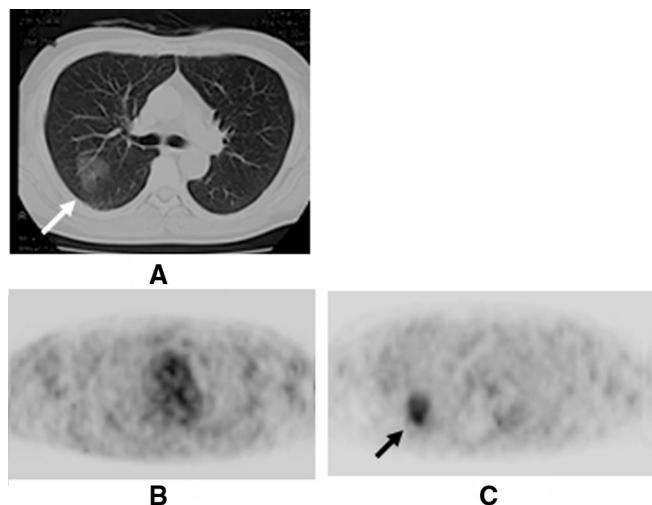


FIGURE 1. Well-differentiated adenocarcinoma with ground-glass opacity findings. A, Computed tomographic findings. B, ^{18}F -fluorodeoxy-glucose-positron emission tomography showed negative. C, ^{11}C -acetate-positron emission tomography showed positive. An arrow shows the image of tumor.

RESULTS

AC-PET usually identified W/D adenocarcinomas more clearly than FDG-PET (Figure 1). AC-PET also identified other types of NSCLC and FDG-PET (Figure 2). The ROC curve for the discrimination between NSCLC and benign nodules showed the optimal SUV-CR cutoff value to be 1.35 for AC-PET and 1.66 for FDG-PET (Figure 3).

Table 2 shows the correlation between AC- and FDG-PET for the diagnosis of NSCLC. The sensitivity of AC-PET was 0.71 (95% confidence interval [CI]: 0.65–0.77), which was significantly higher than the value of 0.57 (95% CI:

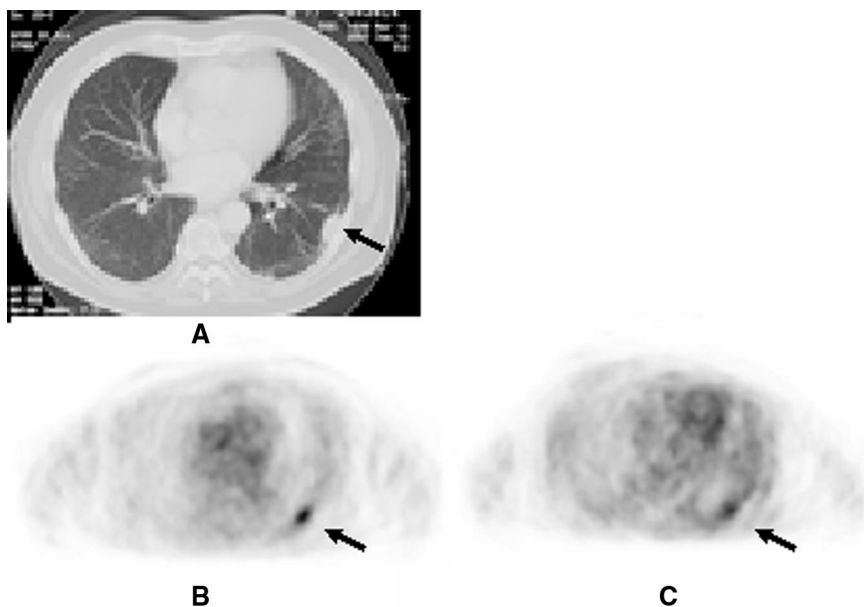


FIGURE 2. Squamous cell carcinoma. A, Computed tomographic findings. B, ^{18}F -fluorodeoxy-glucose-positron emission tomography showed positive. C, ^{11}C -acetate-positron emission tomography showed positive. An arrow shows the image of tumor.

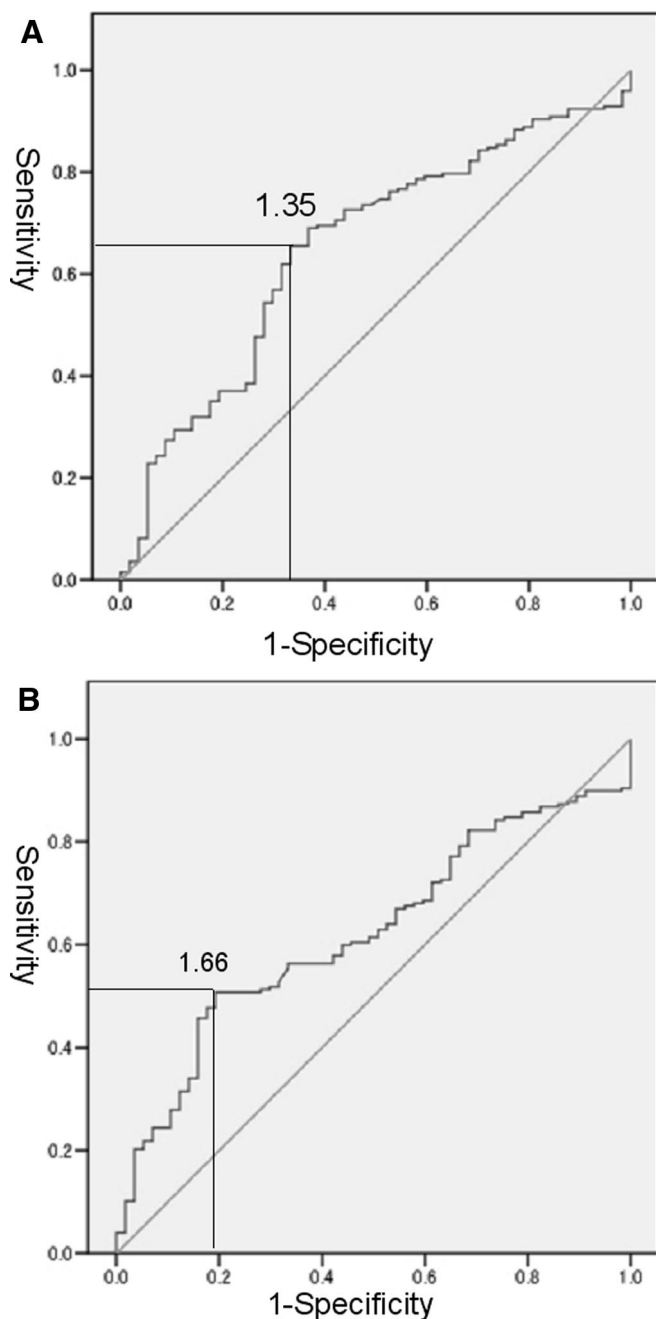


FIGURE 3. The receiver operating characteristics curve of contrast ratio of standard uptake value (SUV-CR) for diagnosing non-small cell lung cancer. *A*, Acetate-positron emission tomography. Cutoff value of SUV-CR is 1.35 (sensitivity: 0.69, 1-specificity: 0.37, area under curve: 0.65, 95% confidence interval: 0.57–0.73). *B*, ^{18}F -fluorodeoxy-glucose-positron emission tomography. Cutoff value of SUV-CR is 1.66 (sensitivity: 0.57, 1-specificity: 0.19, area under curve: 0.62, 95% confidence interval: 0.55–0.70).

0.51–0.63) obtained by FDG-PET (McNemar test: $p < 0.001$). Table 3 shows the correlation between AC- and FDG-PET for the diagnosis of benign nodules. The specificities of AC- and FDG-PET were 0.70 (95% CI: 0.58–0.82)

TABLE 2. Correlation between Acetate-PET and FDG-PET for Diagnosis of Non-small Cell Lung Cancer

FDG-PET	Acetate-PET		Total
	True-positive	False-negative	
True-positive	114	15	129
False-negative	47	51	98
Total	161	66	227

FDG, fluorodeoxyglucose; PET, positron emission tomography.
Sensitivity of acetate-PET: 0.71 (95% confidence interval: 0.65–0.77).
Sensitivity of FDG-PET: 0.57 (95% confidence interval: 0.51–0.63).
McNemar test: $p < 0.001$.

TABLE 3. Correlation between Acetate-PET and FDG-PET for Diagnosis of Benign Pulmonary Nodules

FDG-PET	Acetate-PET		Total
	True-negative	False-positive	
True-negative	38	6	44
False-positive	2	11	13
Total	40	17	57

FDG, fluorodeoxyglucose; PET, positron emission tomography.
Specificity of acetate-PET: 0.70 (95% confidence interval: 0.58–0.82).
Specificity of FDG-PET: 0.77 (95% confidence interval: 0.66–0.88).
McNemar test: $p = 0.29$.

TABLE 4. Correlation between Acetate-PET and FDG-PET for Diagnosis of Each Histologic Type of Non-small Cell Lung Cancer

FDG-PET	Acetate-PET		Difference
	True-positive	False-negative	
W/D adenocarcinoma ($n = 146$)			
True-positive	47	7	
False-negative	43	49	$p < 0.001$
M/D or P/D adenocarcinoma ($n = 51$)			
True-positive	39	7	
False-negative	4	1	$p = 0.55$
Nonadenocarcinoma ($n = 30$)			
True-positive	28	1	
False-negative	0	1	$p = 1.0$

FDG, fluorodeoxyglucose; PET, positron emission tomography; W/D, well-differentiated; M/D, moderately-differentiated; P/D, poorly-differentiated.

and 0.77 (95% CI: 0.66–0.88), respectively; this difference was not significant (McNemar test: $p = 0.29$).

Table 4 shows the AC- and FDG-PET findings in each histologic type of NSCLC. For the 146 W/D adenocarcinomas, the sensitivity of AC-PET was 0.62, which was significantly higher than the value of 0.37 obtained by FDG-PET (McNemar test: $p < 0.001$). For the 51 M/D or P/D adenocarcinomas, the sensitivities of AC- and FDG-PET were 0.84 and 0.90, respectively; this difference was not significant

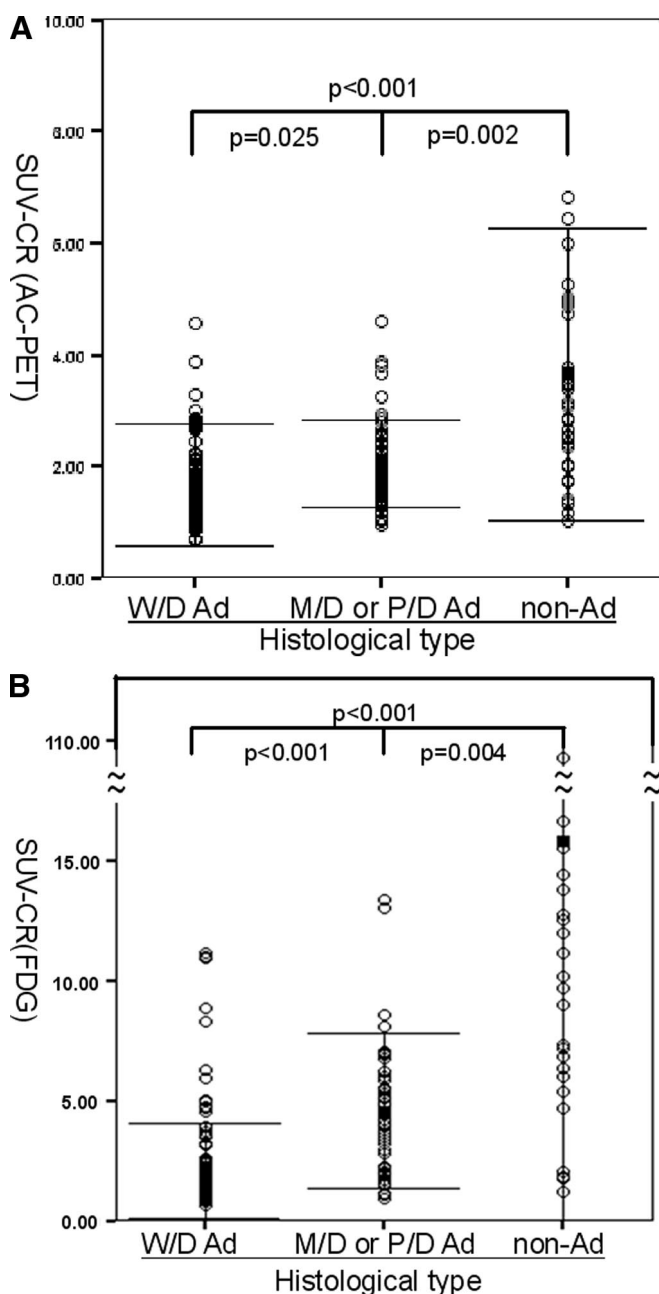


FIGURE 4. Distribution of SUV-CR for (A) ^{11}C -acetate-positron emission tomography and (B) ^{18}F -fluorodeoxy-glucose-positron emission tomography among each histologic types of non-small cell lung cancer. SUV-CR, contrast ratio of standard uptake value.

(McNemar test: $p = 0.55$). For the 30 nonadenocarcinomas, the sensitivities of AC- and FDG-PET were 0.93 and 0.97, respectively; this difference was not significant (McNemar test: $p = 1.0$). In the AC-PET, the positive rates for W/D adenocarcinoma (62%) was significantly lower than those for M/D or P/D adenocarcinomas (86%) and nonadenocarcinomas (93%) ($p = 0.003$ and 0.001 , respectively). In the FDG-PET, the positive rates for W/D adenocarcinomas

(37%) was significantly lower than those for M/D or P/D adenocarcinomas (90%) and nonadenocarcinomas (97%) (both, $p < 0.001$).

Figure 4 shows the distribution of the SUV-CR values for AC-PET and FDG-PET according to each histologic type. The mean SUV-CR values for W/D adenocarcinomas, M/D or P/D adenocarcinomas, and nonadenocarcinomas obtained by AC-PET were 1.7 ± 1.1 , 2.0 ± 0.8 , and 3.8 ± 2.7 , respectively (Figure 4A), whereas those obtained by FDG-PET were 2.1 ± 2.0 , 4.5 ± 3.2 , and 16 ± 20 , respectively (Figure 4B). M/D or P/D adenocarcinomas and nonadenocarcinomas had a significantly higher SUV-CR values than W/D adenocarcinomas in both the AC-PET ($p = 0.025$ and $p < 0.001$, respectively) and FDG-PET (both $p < 0.001$). Nonadenocarcinomas also had a significantly higher SUV-CR value than M/D or P/D adenocarcinoma in both the AC- and FDG-PET ($p = 0.002$ and 0.003 , respectively).

DISCUSSION

The present study showed that AC-PET had significantly higher sensitivity for diagnosing W/D adenocarcinomas than FDG-PET, whereas there was no significant difference of sensitivity for diagnosing M/D or P/D adenocarcinomas and nonadenocarcinomas between the two. There was no significant difference of specificity between the two. We therefore concluded that AC-PET can be used in place of FDG-PET for the imaging NSCLC, with higher sensitivity for W/D adenocarcinomas.

Although the mechanism underlying ^{11}C -AC-uptake in tumor cells has not been clarified sufficiently, Yoshimoto et al.,¹⁶ in an in vitro study using several cancer cell lines, reported that the ^{14}C -AC level in the lipid-soluble fraction of the tumor cells was positively correlated with the tumor growth activity measured by ^3H -thymidine uptake; therefore, they suggested that AC was preferentially metabolized to membrane lipids in tumor cells and that AC-uptake by the tumor cells reflects their growth activity, which could be paralleled to the enhanced membrane synthesis. On the other hand, AC-PET has been reported to be able to image slow-growing tumors, such as W/D hepatocellular carcinoma, prostate cancer, and thymoma, which often show negative imaging with FDG-PET.^{9–11} In the present study, although the W/D adenocarcinomas could be imaged by AC-PET more frequently than by FDG-PET, they showed less positive rates and less SUV-CR values than M/D or P/D adenocarcinomas or nonadenocarcinomas in both the AC- and FDG-PET. Based on these data, we have made the following hypotheses explaining AC- and FDG-uptake in NSCLC: (1) whereas FDG would hardly accumulate in W/D adenocarcinomas because of their low glucose metabolism, AC might accumulate in them, probably because they metabolize AC for membrane lipid synthesis; and (2) aggressive adenocarcinomas like M/D or P/D adenocarcinomas and nonadenocarcinomas would metabolize both AC and FDG actively for both membrane lipid synthesis and glucose metabolism, respectively.

Although SUV-max has frequently been used to evaluate FDG-PET, several factors have been reported to

affect the SUV-max, such as body size¹⁷ and blood glucose level.^{18,19} We previously compared the results of SUV-max, SUV-CR with the contralateral lung, and SUV-CR with the cerebellum for pulmonary nodules, and reported that the SUV-CR with contralateral lung or cerebellum was significantly more sensitive than the SUV-max⁴; this result was further supported in a study by Obrzut et al.²⁰ Besides, because two kinds of PET scans were used in the present study, we used the SUV-CR with the contralateral lung to dissolve the possible difference of SUV measurement between the two PET scans.

The area under the curve on ROC curve obtained by FDG-PET in the present study was not large enough, compared with our previously reported one,² that would be likely attributable to the followings: Because the purpose of the present study was to compare the sensitivity and specificity between AC- and FDG-PET in patients with lung adenocarcinoma or lesions suspected of lung adenocarcinoma, 146 of the 229 (64%) adenocarcinomas were W/D adenocarcinomas that produced negative FDG-PET results more frequently than other histologic types of NSCLC, resulting in a small area under the curve on the ROC curve.

The present study showed that AC-PET was superior to FDG-PET for the imaging of W/D adenocarcinomas and was equal with FDG-PET for the imaging of other histologic types of NSCLC. AC-PET has the following advantages over FDG-PET: (1) patients do not have to fast before examination; (2) radiation exposure from ¹¹C-AC is less than that from ¹⁸F-FDG because the half life is much shorter (20 minutes versus 120 minutes); and (3) less time is required for the examination (20 minutes for AC-PET versus 90 minutes for FDG-PET). We therefore consider that AC-PET can be used in place of FDG-PET for imaging NSCLC, with higher sensitivity for W/D adenocarcinomas compared with FDG-PET.

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APPENDIX

The following investigators participated in the study: H. Nomori, H. Shibata, T. Iyama, Y. Honda: Graduate School of Medical and Pharmaceutical Sciences, Kumamoto University; T. Goya: Kyorin University Hospital; I. Takanami: Teikyo University Hospital; T. Suzuki: Showa University Fujigaoka Hospital; K. Koizumi: Nihon Medical University Hospital; M. Kaji: Saiseikai Central Hospital; H. Horio: Tokyo Metropolitan Komagome Hospital; K. Uno, K. Kazuya: Nishidai Clinic, Tokyo, Japan; R. Nakashima: Japanese Red Cross Kumamoto Health Care Center.

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